REMARKS

Claims 1, 2, 5-11, 13, 19, and 20 are pending in this application. New claims 21-23 have been added to the application. Therefore, claims 1, 2, 5-11, 13, and 19-23 are at issue.

New claims 21 and 22 have been added to recite specific sexual dysfunctions treated by an article of the present invention. Support for claims 21 and 22 can be found in the specification at page 9, lines 21-27. Support for new claim 23 can be found in originally filed claim 9, for example.

This response is filed to reply to the examiner's new grounds of rejection and the examiner's comments and arguments set forth in the Office Action of June 4, 2003. The claimed invention, the form of the claims, and the reasons why the present claims would not have been obvious over the cited references were thoroughly discussed at pages 6-26 of Amendment "B," filed January 14, 2003. For the sake of brevity, many of the arguments and much of the reasoning set forth in Amendment "B" are not fully reiterated herein, but are incorporated into this response by reference.

> A. "Claims 1-2, 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daugan et al. (WO 96/32003)
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> Daugan et al. (WO 96/32003) teaches a pharmaceutical composition comprising a PDE5 inhibitor compound of Formula I, see abstract. Daugan et al. (WO 96/32003) teaches that its pharmaceutical composition can be used to treat erectile dysfunction, see particularly page 7, line 34 and page 8, line 1. Daugan et al. (WO 96/32003) shows that

the compounds of formula I exhibit an IC_{50} value of less than 10 mM, see particularly Table 1. Daugan et al. (WO 96/32003) also teaches that the preferred route of administration is oral, and that the dosage range is from 0.5-800 mg, individual tablets contain from 0.2-400 mg of the active compound in a suitable pharmaceutically acceptable carrier, for administration in single or multiple doses, once or several times per day (which may constitute chronic administration), see particularly page 9, lines 5-11. Daugan et al. (WO 96/32003) also teaches that its pharmaceutical composition can be used in treating cardiovascular disorders, e.g., conditions of reduced blood vessel patency, peripheral vascular disease, see particularly page 7, line 21 to page 8, line 2.

Daugan et al. (WO 96/32003) does not teach the inclusion of a package insert or a container.

It would have been obvious to one of ordinary skill at the time the invention was made to include the PDE5 active herein in a container and to include the package insert herein for the therapeutic composition.

One of ordinary skill in the art would have been motivated to include the therapeutic agent comprising PDE5 in a container since the packaging of pharmaceutical compositions is widely practiced in the art and is therefore within the skill of the artisan. Moreover, the inclusion of a package insert including "indications and use" of the pharmaceutical composition is mandated by 21 CFR 201.57 and is therefore obvious to one of ordinary skill in the art (see *Remington's: the Science and Practice of*

Pharmacy, Nineteenth Edition, Vol. 1, page 806)."

In short, the examiner contends that it would have been obvious to utilize a compound of WO '003 in a container with a package insert, and that a package insert is mandated therefor. In view of the arguments set forth in Amendment "B," and for the following reasons, it is submitted that this rejection is in error and should be withdrawn.

WO '003 discloses a PDE5 inhibitor capable of treating numerous diseases and conditions, including erectile dysfunction. The examiner relies upon WO '003 for a teaching of a PDE5 inhibitor having an IC_{50} value less than 10 nM, oral administration, and a dosage of 0.5-800 mg (e.g., 0.5-400 mg in tablets) for administration "once or several times per day." However, WO '003 fails to teach or suggest several of the vital claimed features.

For example, an IC_{50} value of less than 10 nM *alone* is not sufficient to render a compound suitable for use in the present invention. The PDE5 inhibitor also must have a sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages, and, in preferred embodiments, at a maximum daily dose of about 10 mg. Neither this cited reference, nor any other reference of which applicants are aware, teaches or suggests these features.

Bioavailability is a property of a compound that is independent from its IC_{50} value. The IC_{50} value is related to potency of a compound in inhibiting the PDE5 enzyme in an *in vitro* assay. Bioavailability is an *in vivo* property wherein the *physical and pharma-*

cologic properties of the compound, e.g., *in vivo* solubility, are such that the compound is made available in the body to inhibit PDE5.

WO '003 fails to teach or suggest, and does not even consider or address, the bioavailability of the compounds disclosed therein. More importantly, WO '003 does not teach or suggest that the combination of IC_{50} value and bioavailability can be used to provide a low chronic dosage to treat sexual dysfunction. In particular, persons skilled in the art are aware of many compounds having a low IC_{50} value, but insufficient bioavilability, such that the compound is ineffective for its proposed use. Therefore, the teaching in WO '003 of a compound having an IC_{50} value less than 10 nM is insufficient to provide a compound useful in a present article of manufacture.

In addition, WO '003 fails to teach a PDE5 inhibitor for chronic administration having the properties recited in dependent claim 5, which together with the features recited in claims 1 and 2, claim especially preferred compounds for use in the present invention. It must be understood that an IC_{50} value (i.e., potency) also is entirely independent from the differential IC_{50} values (i.e., selectivity) recited in claim 5. WO '003 fails to teach or suggest compounds having the inhibition selectivity recited in claim 5, and fails to recognize the advantages and importance of such PDE inhibition selectivity.

Furthermore, WO '003 merely teaches a dosage that can be administered either once per day or in multiple doses over the course of a day, i.e., "once or several times *per* day." WO '003 is totally silent with

respect to a chronic administration, e.g., daily administration for at least three consecutive days, to treat erectile dysfunction using a chronic low dosing regimen of about 1 to about 10 mg, and, preferably, a maximum dosage of about 10 mg/day, but rather teaches an "on demand" regimen using a relatively high dosage of PDE5 inhibitor.

The examiner's statement that inclusion of a package insert including "indications and use" of a pharmaceutical compound is obvious because of the Remington publication is irrelevant. The examiner has failed to consider the indicia on the presently claimed insert, and its functional relationship to the oral dosage form, i.e., that the claimed oral dosage form is used in a chronic administration regimen to treat sexual dysfunction and improve vascular conditioning. Without the insert and the *claimed* indicia thereon, the user of the article would not be informed of the new and nonobvious function of the low oral dose form of PDE5 inhibitor present in the article of manufacture. In particular, applicants are not attempting to patent the printed matter on the insert, but *all* recited components (a)-(c) in the independent claims, and the additional recited features in the dependent claims.

The present invention relies on the discovery that improved vascular conditioning results from a chronic administration of a PDE5 inhibitor as defined in claims 1(a), 2(a), 19(a), and 20(a), for example, and in the dependent claims in particular. This improved vascular conditioning is useful in treating sexual dysfunction when administered in a chronic regimen, as set forth on the claimed package insert.

The present claims are both novel and nonobvious over WO '003 and other articles of manufacture for treating erectile dysfunction.

In particular, the novelty of the present claims does not lie in the mere presence of a container and an insert, but upon the identity of the PDE5 inhibitor, as defined in paragraph (a) of claims 1, 2, 19, and 20, in the container, *and* upon the *functional information* in the package insert, i.e., a chronic dosing regimen for treating erectile dysfunction. There is no known article of manufacture, or reference, that teaches or suggests these claimed features.

In summary, WO '003 discloses PDE5 inhibitors for treating erectile dysfunction and provides a broad oral dosage range for an on-demand treatment regimen. WO '003 neither teaches nor suggests a chronic dosing regimen, e.g., for at least three consecutive days, preferably by the administration of up to 10 mg/day of a claimed PDE5 inhibitor. WO '003 teaches *dividing* a daily dose into multiple doses, but fails to teach or suggest consecutive chronic, or daily, doses in a low dosage amount. In fact, WO '003 merely teaches the only method of treating sexual dysfunction using a PDE5 inhibitor known at that time, i.e., an "on demand" administration of a PDE5 inhibitor at a high dosage rate.

As understood in the art, "on demand" means an individual ingests a sufficient amount of a PDE5 inhibitor prior to a preplanned sexual activity. This "sufficient amount" can vary among individuals, and is determined by the individual and the individual's physician taking into account the response of the

individual to a particular dose of the PDE5 inhibitor. In the case of a male, after a latency period, the individual then is capable of achieving a sufficient erection for sexual intercourse. The effect of the PDE5 inhibitor diminishes over the course of a few to several hours and the ability to achieve a sufficient erection for intercourse is lost. This cycle is repeated prior to next preplanned sexual activity, whether that time period is the next day or the next month.

In a "chronic" dosing regimen, the need to preplan sexual activity is eliminated. Due to the vascular conditioning provided by the present invention, a low chronic dose of a claimed PDE5 inhibitor, termed herein a "sub-effective dose" for a particular individual, allows spontaneous sexual activity. In addition, it surprisingly has been found that the amount of PDE5 inhibitor present in the blood stream after chronic administration of this low dose of PDE5 inhibitor *is greater* than that after administration of a high "on-demand" dosage of PDE5 inhibitor.

The cited WO '003 reference fails to teach or suggest a chronic dosing regimen, and no presently available PDE5 inhibitor treatment utilizes a chronic dosing regimen. WO '003 absolutely fails to provide any motivation for a person skilled in the art to consider a chronic dosing regimen as claimed, and provides no incentive for a person skilled in the art to reduce the PDE5 inhibitor dosage to about 1 to about 10 mg with any reasonable expectation of providing an article of manufacture useful in the treatment of sexual dysfunction.

In addition, the presently claimed invention not only meets an unsatisfied need in the art, i.e., a treatment of sexual dysfunction that permits more normal sexual relations with respect to spontaneity and avoiding the need to preplan sexual activity, but the low dose of PDE5 inhibitor also reduces or eliminates various adverse side effects associated with a higher dose of a PDE5 inhibitor used to treat sexual dysfunction on demand. Accordingly, it is submitted that the rejection of pending claims 1, 2, and 5-9 as being obvious over WO '003 is in error and should be withdrawn.

Applicants also strongly traverse the examiner's contention that the administration of single or multiple doses, "once or several times a day," constitutes a chronic administration. At the time of filing WO '003, the only treatment for sexual dysfunction using a PDE5 inhibitor was an "on-demand" dose of a sufficient amount of the PDE5 inhibitor to allow the treated individual to achieve an erection. The dosage amount of PDE5 inhibitor can vary from individual to individual. Once below a critical concentration, the PDE5 inhibitor does not treat sexual dysfunction. As previously stated, after a sufficient latency period for the PDE5 inhibitor to enter the blood stream, the inhibitor treats sexual dysfunction. Treatment continues for a time period as long as the PDE5 inhibitor is present in the blood stream in a sufficient concentration to treat sexual dysfunction.

In an "on-demand" treatment, it is incumbent to administer a sufficiently large PDE5 inhibitor dose to the individual to treat the sexual dysfunction. An

insufficient dose would be ineffective in treating sexual dysfunction. The present invention provides a substantial advance in the art by allowing the administration of a dose less than the dose considered effective in an "on-demand" regimen (termed herein a "sub-effective" dose). In accordance with the present invention, after a sufficient number of "sub-effective" doses, i.e., a chronic dosing regimen, the individual has successfully treated sexual dysfunction. Continuing the administration of "sub-effective" doses maintains the treatment, which in effect allows spontaneous, as opposed to planned, sexual activity. If the individual ceases the chronic treatment, the advantages of the chronic treatment regimen are lost. The individual must either start a chronic regimen again, or rely upon an "on-demand" regimen using a higher dose of PDE5 inhibitor.

As also previously stated, it is surprising that the low chronic dose results in a greater circulating concentration of the PDE5 inhibition than a larger "on-demand" dose. This surprising result has been attributed to an improved vascular conditioning resulting from the chronic administration of a claimed PDE5 inhibitor.

In summary, WO '003 merely discloses dividing a large PDE5 inhibitor dose into a smaller dose to provide a correct "on-demand" treatment dose, or administering several small doses to provide the correct "on-demand" treatment dose. WO '003 absolutely fails to teach or disclose a "sub-effective" dose *in a chronic regimen* to treat sexual dysfunction in a continuous manner, rather than in a sporadic, "on-demand," manner.

B. "Claims 1-2, 5-11, 13, 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daugan WO 97/03675 (submitted by the applicant in the parent application 09/558911, August 29, 2001), and *Remington: The Science and Practice of Pharmacy* (of record in the previous office action).

Daugan teaches compounds of formula I (which reads on formula I of the instant application) in general and the two particular compounds recited in claim 10 herein in an article useful in treating erectile dysfunction in a dose of 0.5-800 mg/day, see abstract, claim 4 and page 5 in particular. Daugan also teaches that its composition can be administered in single or multiple doses, once or several times a day, see page 5.

WO 97/03675 does not teach the inclusion of a package insert, nor does it disclose a container.

It would have been obvious to one of ordinary skill at the time the invention was made to include the PDE-5 active herein in a container and to include the package insert herein for the therapeutic composition.

One of ordinary skill in the art would have been motivated to include the therapeutic agent comprising PDE5 herein in a container since the packaging of pharmaceutical compositions in articles is widely practiced in the art and is therefore within the skill of the artisan. Moreover, the inclusion of a package insert including 'indications and use' of the pharmaceutical composition is mandated by 21 CFR 201.57 and is therefore obvious to one of ordinary skill in the art. (See *Remington's: the Science and Practice of Pharmacy*, Nineteenth Edition, Vol. 1, page 806)."

In view of the arguments set forth in Amendment "B," for all the reasons set forth above, and for the reasons set forth below, it is submitted that this rejection is in error and should be withdrawn.

Like WO '003, WO '675 teaches PDE5 inhibitors and further teaches that the inhibitors are useful in the treatment of sexual dysfunction. Claims 10, 11, and 13 recite compounds disclosed in WO '675. However, WO '675 fails to teach or suggest the claimed invention for the same reasons that WO '003 fails to teach or suggest the presently claimed invention. In particular, there is *no* teaching or suggestion of a claimed chronic dosing regimen, and *no* motivation or incentive for a person skilled in the art to utilize the claimed chronic dosing regimen to treat sexual dysfunction with any reasonable expectation of success.

The combination of Remington's and WO '675 does not render the present claims obvious. Remington's merely teaches that an insert, or label, is required on a pharmaceutical product.[1] All pharmaceutical products require inserts, and all inserts contain directions for use and instructions, but *no* prior insert includes instructions for a chronic regimen to treat sexual dysfunction using a low dose of PDE5 inhibitor, as presently claimed.

The fact the 21 C.F.R. 201.57 requires a label is irrelevant. It is not the mere fact of having an insert as a component of the article that is impor-

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[1] However, the Remington reference is *silent* with respect to the *specific* information that must be on the label, including, but not limited to, conditions treated, dosages, dosing regimens, warnings, and contraindications.

tant. What is important is the indicia on the insert and how it functionally relates to the oral dosage form and how it instructs individuals to treat sexual dysfunction in a new and unexpected manner, i.e., the claimed chronic dosing regimen using the specifically claimed PDE5 inhibitors. The insert and indicia thereon must be considered with *all* other claimed features, as set out in the case law discussed in Amendment "B."

The presently claimed PDE5 inhibitors, at a low chronic dose, exhibit an ability to improve vascular conditioning, and they remain in the plasma to a sufficient extent, and for extended periods, to allow an effective chronic dosing regimen for the treatment of sexual dysfunction, as discussed above.

Accordingly, it is submitted that all pending claims are patentable under 35 U.S.C. §103 over the combination of WO '675 and Remington's, for the above reasons and for the reasons the present claims are patentable over WO '003, and that this rejection is in error should be withdrawn.

> C. "Applicant's arguments with respect to the chronic dosage regimen herein have been considered, but are not persuasive. Applicant argues that the claimed invention differs from the cited prior art in that the instant invention requires a chronic dosage regimen. Note that the cited references broadly teach that their compositions can be administered in single or multiple doses, once or several times a day. The teaching of the prior art (specifically '675 patent) is not an on-demand regimen, contrary to the applicant's assertion."

In the above discussion, applicants explained the differences between an "on-demand" and a "chronic" dosing regimen. Applicants also discussed the benefits provided by a chronic dosing regimen compound to an on-demand dosing regimen. However, until the present invention, *no* "chronic" dosing regimen using a PDE5 inhibitor to treat sexual dysfunction has been disclosed or practiced.

The references, as acknowledged by the examiner, merely teach a broad general dosage range of 0.1-800 mg/day for a 70 kg adult. This is a daily dose range and contemplates a sufficiently large dose for a particular compound to be effective in a particular individual in an on-demand regimen. The dose can be taken in single or multiple doses, once or several times *per day*.

The cited references are silent with respect to administering a "sub-effective" dose over the course of *days* to provide an effective treatment for sexual dysfunction. The references merely leave the physician to determine the proper dosing regimen based on age, weight, and response of a particular patient (e.g., WO '003, page 9, lines 11-15). This teaching clearly is directed to an effective "on-demand" dose sufficient to treat sexual dysfunction. From the teachings in the cited references, there is no motivation or incentive for a physician to instruct a patient to use a *less* than effective "on-demand" PDE5 inhibitor dose with any reasonable expectation of successfully treating sexual dysfunction. There also is no motivation or incentive for a physician to instruct a patient to use a less than effective "on-demand" dose in a "chronic" regimen

over a course of consecutive days with any reasonable expectation of providing a successful treatment for sexual dysfunction.

> D. "Applicant then argues that the printed material on the package insert should be given patentable weight. Applicant argues that the instant case is analogous to the *In re Miller* 164 USPQ 46 (CCPA 1969) and *In re Gulack* 217 USPQ 401 (CAFC) 1983. Note that the *Miller* Court relies on the fact that there is a functional relationship between a measuring cup and the indicia (printed material) on the cup. A cup is not a measuring cup without the indicia since one cannot employ the cup (without indicia) to take accurate measurements. The instant case is distinguishable from *Miller* since a patient can take a medication even without having the instructions at hand. The ultimate function of the instant article of manufacture relies not on the instructions, but on the active pharmaceutical ingredient, i.e., the PDE5 inhibitor, contained therein.
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> The Court in *In re Gulack* also states that 'where the printed material is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability.' Here, the set of instructions is not functionally related to the article of manufacture because the article of manufacture can function as an active and effective drug even in the absence of the set of instructions (i.e., package insert). Therefore following the reasoning in *Miller* and *Gulack*, we can conclude that the 'printed material', i.e., the package insert, does not patentably distinguish the instant claims over the prior art."

As stated by the examiner, the *Miller* court relied on the fact that a functional relationship existed between the measuring cup and the indicia on the cup. The examiner relies upon the argument that without indicia on the cup, one cannot take accurate measurements, so a functional relationship existed in *Miller*. However, a person using the cup need *not* use the indicia each time the cup is used. The indicia is present on the cup *when and if* the user desires to refer to the indicia. The user may reference the indicia once, or never. The number of times the indicia is used is irrelevant in a patentability assessment of the measuring cup. It is the cup that is claimed, and that claimed cup must be compared to the prior art. It is not how the user uses the cup, it is the cup itself that was the subject of the patent application, and it is the *cup* that was considered in examining the application and allowing the claims.

Similarly, the indicia on the insert of a presently claimed article of manufacture has a functional relationship to the oral dosage form within the container. In particular, the examiner's statement that the "article of manufacture can function as an active and effective drug even in the absence of the set of instructions" is incorrect. The dose in the presently claimed article of manufacture is a "sub-effective" dose for a majority of individuals, and, therefore, will not act as an effective drug to treat sexual dysfunction in these individuals *without* the indicia present on a claimed insert which directs the individuals to use a chronic dosing regimen.

The indicia on the insert also instructs individuals how to accurately administer the drug, much like the indicia on a measuring cup allows its accurate use. In particular, the measuring cup of *Miller* is still a measuring cup, but it cannot be used accurately without the accompanying indicia. Similarly, the PDE5 inhibitor and its dosage present in the claimed article of manufacture can be administered, but it *cannot* be administered accurately without the accompanying indicia on the insert. Thus, the measuring cup of *Miller* and the presently claimed articles of manufacture are not distinguishable.

In the present claims, a functional relationship exists between the package insert and the oral dosage form, and the claims define this relationship. In particular, the functional relationship is between an oral dosage form containing a *low* dosage of a specifically claimed PDE5 inhibitor and an insert providing that the oral dosage form can be administered chronically to treat sexual dysfunction and to improve vascular conditioning. Without the insert, the user of the claimed article of manufacture would not be informed of the new and unobvious ability to administer a chronic low dose of a claimed PDE5 inhibitor (as opposed to the currently practiced on-demand therapy), and how to use the oral dosage form to effectively treat sexual dysfunction, while avoiding disadvantages associated with on-demand PDE inhibitor therapy for sexual dysfunction. As previously discussed, the cited art is silent with respect to chronic dosing of a PDE5 inhibitor to treat sexual dysfunction.

The examiner's statement that a patient can take a medication without the instructions at hand is conjecture. The patient and/or a physician *must*, or at least *does*, refer to the instructions, dosages, dosage regimen, warnings, and contraindications on the label *at least* before the first use of the medication, and the patient, either directly or by his physician, is *informed* whether the medication can be or should be administered, and how it can be administered.[2] Without the information on a present insert, a patient would not be informed that the article is useful for persons suffering from sexual dysfunction using a low chronic dose of the medication, and that the chronic dosing regimen must be followed to provide an effective treatment for sexual dysfunction.

The insert, therefore, functions to link the PDE5 inhibitor in the low oral dosage form to individuals who now can undergo a chronic PDE5 inhibition treatment for sexual dysfunction. Without the indicia

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[2] The definition of "insert" at page 6, lines 14-21 of the specification states:

> "The term 'package insert' means information accompanying a product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the 'label' for a pharmaceutical product.'

Therefore, the indicia on the label contains functional information with respect to the pharmaceutical product in the container, and is referred to by the patient and/or his physician.

present on a claimed insert, persons would not be informed that such a treatment is available, much like leaving the measuring indicia off of a cup.

In summary, the present claims are both novel and nonobvious over the cited references, alone or in combination, and over other articles of manufacture for treating sexual dysfunction. In particular, novelty of the present claims does not lie in the mere presence of a container and an insert, but upon the identity of the PDE5 inhibitor, as defined in paragraph (a) of the independent claims, *and* upon the *functional information* in the package insert, i.e., a low dosing regimen for the chronic treatment of sexual dysfunction. There is no known article of manufacture, or reference, that teaches or suggests this combination of claimed features.

The cited references, alone or in combination, fail to teach or suggest a claimed article of manufacture, and absolutely fail to provide any motivation for a person skilled in the art to reduce the PDE5 inhibitor to a "sub-effective" dosage rate, and undergo a chronic treatment regimen, with any reasonable expectation of providing an article of manufacture useful in the treatment of sexual dysfunction. In addition, the presently claimed invention meets an unsatisfied need in the art, i.e., a chronic treatment for sexual dysfunction that allows spontaneous sexual activity.

To a person skilled in the art, a presently claimed article of manufacture is not motivated by the cited references, but is discouraged. A person skilled in the art would not have been motivated to provide an

article having a package insert as presently claimed because the art is limited to teaching administration of a sufficiently large dose to provide an "on-demand" treatment. It was the unexpected finding of highly potent and selective PDE5 inhibitors that allow a presently claimed article of manufacture. Further, in this case, it is not only the inclusion of a package insert in the article of manufacture, but also the functional information related to the user (e.g., chronic administration).

In addition, the indicia on a package insert is an element of the claim that must be considered. In particular, the case law states that indicia must be considered with all other claimed elements of a combination.

Accordingly, it is submitted that claims 1, 2, 5-11, 13, and 19-23 would not have been obvious to a person skilled in the art under 35 U.S.C. §103 over WO '003, or the combination of WO '675 and Remington's, and that the rejections should be withdrawn.

It is submitted that all pending claims are in proper form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

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